

## *Depression and associated physical diseases and symptoms*

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*Depression can occur in association with virtually all the other psychiatric and physical diagnoses. Physical illness increases the risk of developing severe depressive illness. There are two broadly different mechanisms. The most obvious has a psychological or cognitive mechanism. Thus, the illness may provide the life event or chronic difficulty that triggers a depressive episode in a vulnerable individual. Secondly, more specific associations appear to exist between depression and particular physical disorders. These may turn out to be of particular etiological interest. The best examples are probably stroke and cardiovascular disease. Finally, major depression, but especially minor depression, dysthymia, and depressive symptoms merge with other manifestations of human distress with which patients present to their doctors. Such somatic presentations test the conventional distinction between physical and mental disorder, and are a perennial source of controversy.*

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**D**epression is sometimes described as the “common cold” of psychiatry. It is certainly common, and it is also present most commonly in mild forms, which extends the analogy somewhat. However, in its most severe forms it is the major problem that may preoccupy any ill patient—to the point where he or she may commit suicide. Indeed, a formal major depressive episode can occur in association with virtually all the other psychiatric and physical diagnoses. This review will address primarily physical illnesses.

Physical illness increases the risk of developing severe depressive illness. There are two broadly different mechanisms that may explain this, which are not mutually exclusive. The first is the most obvious, probably the most common, and is usually described as having a psychological or cognitive mechanism. It may be understandable as the threat that any severe and/or chronic illness may pose to an individual’s sense of purpose and meaning in life. Thus, the illness may provide the life event or chronic difficulty that triggers a depressive episode in a vulnerable individual. Physical illness may thereby be a component of the complex pathway that determines the emergence of depression. The mechanisms may be both genetic and nongenetic, and have been best teased out by twin studies, primarily in women.<sup>1-3</sup> Such an association between depression and physical illness may be highly nonspecific and unbiological. However, this cannot be assumed axiomatically to be true. Indeed, all severe depression is in some sense biological, and some unexpected associations may be mediated by a biology that is related to both the physical illness and to the systems that support depressive reactions. Examples of the more specific association will be given below; they may turn out to be of particular etiological interest.

In addition, major depression, but especially minor depression, dysthymia, and depressive symptoms merge

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## Selected abbreviations and acronyms

<b>CBT</b>	<i>cognitive behavioral therapy</i>
<b>CFS</b>	<i>chronic fatigue syndrome</i>
<b>FM</b>	<i>fibromyalgia</i>
<b>IBS</b>	<i>irritable bowel syndrome</i>
<b>MCS</b>	<i>multiple chemical sensitivity</i>
<b>MI</b>	<i>myocardial infarct</i>
<b>SSRI</b>	<i>selective serotonin reuptake inhibitor</i>

with other manifestations of human distress, with which patients present to their doctors. Such somatic presentations test the conventional distinction between physical and mental disorder, and are a perennial source of controversy. While it will not be possible to do the topic full justice, the key issues will be noticed.

## Depressive illness and stroke

After severe stroke, it has been suggested that depression is more common and, more critically, that the particular site of the brain insult may influence the risk of subsequent mood disorder. Thus, a nonspecific risk from the problems posed by disability may be compounded by a more specific neuropsychiatric impact, depending on the localization of the lesion. The obvious problem is that both the disability and the putative direct impact on depression neurobiology might be expected to vary with the localization, and inevitably confound one explanation with the other.

The original stroke studies recruited patients requiring hospital admission and longer-term care. They suggested an association between depression and the left frontal pole regions, and euphoria and right hemisphere lesions.<sup>4</sup> In fact such stroke events may be unrepresentative of cerebrovascular events in general; confirmation in more representative cases with less severe disability would have been interesting. In fact, the story remains a little confused. In an unselected series of patients recruited from the community, in the 12 months after stroke, “emotionalism” occurred in 10% to 20% and was associated with left-sided anterior lesions<sup>5</sup> but there were few cases of major depression. However, subsequently, the same study was written up much more negatively.<sup>6</sup> A comparably negative study has been reported using a similar sample of stroke patients.<sup>7</sup> The rates of depression vary between series<sup>8</sup> and are likely to be influenced by a range of general risk factors for depression. These might be expected to often swamp the effects of the site of lesion.<sup>9</sup>

Certainly, it would be misleading to suggest that there exists a particularly consistent relationship between most strokes and depression.

Nevertheless, in an appropriate case-control series, there could be associations between lesion location and risk of depression that would be of neurobiological interest. For example, lesions in the region of the left basal ganglia have been suggested to be more specifically associated with depression.<sup>10</sup> Larger community studies of cardiovascular disease (not stroke per se) have also suggested an association between depressive symptoms and lesions of the basal ganglia.<sup>11</sup>

Whatever the etiology, depression is of appreciable practical importance for the management of stroke patients who develop it.<sup>12</sup> Depressive symptoms shortly after stroke (not major depression itself) predict increased mortality in unselected stroke patients.<sup>13</sup> Pharmacological treatment of post-stroke depression has been subjected to a number of small controlled trials. The evidence is that antidepressants are effective, although some tricyclics may be prone to produce confusion, so selective serotonin reuptake inhibitors (SSRIs) or other less toxic medicines are probably preferable.<sup>14</sup>

## Heart disease

Findings in patients with myocardial infarction (MI) who show depressive symptoms have also proved interesting. There appears to be an association between short-term mortality following MI and the presence of significant depressive symptoms in the acute-care setting. For example, in 222 patients interviewed between 5 and 15 days following the MI and followed up for 6 months, depression was a significant and independent predictor of mortality from cardiac causes (95% confidence interval [CI], 4.61 to 6.87).<sup>15</sup> The effect was confirmed at 18 months.<sup>16</sup> Indeed, it is sometimes claimed that a depression questionnaire is more informative than an intracardiac electrocardiogram (ECG)! Depressive symptoms are also associated with increased medical comorbidity post-MI, which is a further mechanism likely contributing to a poor outcome.<sup>17</sup> The depressive syndrome following MI has not been sufficiently characterized, but one small study has suggested atypical features.<sup>18</sup>

Traditionally, it might be supposed that depressive symptoms after MI would be reactive and psychological in origin. It would be easy enough to construct the usual plausible story. In fact, there is evolving evidence that

depressive symptoms can predict an elevated risk of MI many years *before it occurs*<sup>19</sup> and/or in the few weeks before an acute admission<sup>20</sup> A follow-up of the Baltimore cohort of the Epidemiologic Catchment Area (ECA) study showed that, compared with respondents with no history of dysphoria, the odds ratio for MI associated with a history of dysphoria was 2.07 (95% confidence interval [CI], 1.16 to 3.71), and with a history of major depressive episode was 4.54 (95% CI, 1.65 to 12.44), independent of coronary risk factors.<sup>21</sup> A recurrence detected in the coronary care unit may carry a particularly poor prognosis.<sup>22</sup> Patients with severe affective disorder have been known to have an increased mortality from cardiovascular causes for a long time (eg, ref 23, 24) and the nature of the association between the two is of considerable evolving interest. The most common cause of death is probably cardiac arrhythmia.<sup>16</sup> It may be relevant that depressed patients with stable heart disease have higher resting heart rates and lower variability during ordinary activity.<sup>25</sup> Autonomic dysfunction may be the cause of subsequent fatal arrhythmia. Thus, it is possible, as with stroke, that some patients show an association between heart disease and depression that is biological in origin. The control of autonomic function may colocalize with limbic representations of stress, anxiety, and mood. If so the complex temporal associations between MI events and depression could originate from common central representations. Unfortunately for the generality of this idea, recent findings in stable patients with ischemic heart disease showed no relationship between depression and heart rate variability indices.<sup>26</sup>

If patients with heart disease are depressed, how should they be treated? One influential idea has been that serotonin may provide the common factor between MI and depression. The logic is a little tortuous since MI is putatively associated with *increased* platelet function under the influence of serotonin, and depression with *reduced* serotonin function centrally. However, SSRIs might simultaneously increase central nervous system (CNS) serotonergic function while depleting the platelet of serotonin.<sup>27</sup> The SADHEART study compared the SSRI sertraline with placebo in patients with recent MI or unstable angina. It showed reduced depressive symptoms after sertraline, especially in more depressed patients. However, cardiovascular benefits were not discriminable, although the trial was underpowered to detect worthwhile differences in rates of severe events.<sup>28</sup> SSRIs are usually regarded as first line, primarily on safety grounds. Clearly, the fact of recent

myocardial infarction is a reason for cautious prescribing, but the field rests primarily on precautionary principles rather than a wealth of trial data.<sup>29</sup>

A psychological intervention might appear more logical than drug treatment on safety grounds alone, but experience has been mixed: effects in one study of behavior therapy were positive for hostility but negative for depression<sup>30</sup>—a potentially undesirable outcome. In the longer term, it has proved difficult to show an effect of treatment for depression on cardiac outcomes.<sup>31</sup>

### Depression in association with nonspecific somatic complaints; chronic pain, fibromyalgia, and chronic fatigue

Depressive symptoms, and depressive syndromes, are seen more commonly in association with a variety of conditions that often have physical or somatic presentations. There are a range of these disorders with much in common, both with each other and with low-level depression. They include a variety of chronic pain states, fibromyalgia, and chronic fatigue. One could also add, although they will not be much addressed here, irritable bowel syndrome, multiple chemical sensitivity, and some of the “syndromes” associated with army service (eg, “Gulf War syndrome”).

The common factor is usually chronic pain or discomfort, and, one may add, a general uncertainty about the etiology. It hard to know whether separate symptoms or syndromes represent cause or effect. Indeed, the different medical traditions converging on these patients frequently take oddly polarized views about the causality, and even whether such patients are really ill. It is the kind of disagreement also much beloved of the popular press. Such medical confusion is inevitably likely to confound the sentiments of patients who are themselves uncertain whether they are really ill, or consciously or unconsciously have something to gain from the sick role. It would be impossible to do full justice to the debate that rages around a diagnosis such as chronic fatigue or Gulf War syndrome in a short chapter on depression. Instead, it may be more useful to notice how depression may be related to the more obvious symptoms that characterize the various syndromes.

### Minor depression, dysthymia, and depressive personality

The problem starts with minor depression. Minor depressive states have long presented a diagnostic confusion. Efforts to wring meaningful classifications out of minor

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symptoms, present to a greater or lesser degree, either with more obvious temperamental abnormality or with more prominent anxiety or somatic symptoms, remain of dubious clinical value. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*) includes a category of mood disorder described as dysthymia, where a few depressive symptoms are present for over 2 years. As well as those symptoms contributing to a diagnosis of major depression, there are features such as pessimism, low self-esteem, low energy, irritability, and decreased productivity. These clinical cases would previously have been subsumed under the notion of neurasthenia or depressive personality<sup>32</sup> but their credibility has been increased by the reports of responsiveness to pharmacological treatment.<sup>33,34</sup> Medicines of greater specificity and lower side-effect profile than tricyclic antidepressants and old-style monoamine oxidase inhibitors (MAOIs) have made treatment feasible. The diagnosis can also be made in patients with superimposed major depression.

What of depressive personality disorder? Personality disorder is defined to be present from adolescence and invariant, more or less, throughout life. Akiskal has argued that temperament is critical to understanding the spectrum of chronic affective disorder,<sup>35</sup> so echoing an earlier generation of clinicians who saw illnesses as reactions by personality types.<sup>36</sup> Measures of personality such as neuroticism are stable across the adult lifespan<sup>37</sup> and predict vulnerability to depression.<sup>3</sup> Personality dimensions seem to require continua not categories, and the diagnosis of discrete syndromes would in general be enriched by systematic measures of personality or other dispositions.

Minor states can only really be understood in relation to population norms from appropriate large-scale representative studies. There appears to be a more or less continuous distribution between the well and the ill with regard to a range of measures of subjective distress, particular symptoms or groups of symptoms, duration, and degree of impairment. Where one sets the threshold for the definition of “a case of depression” therefore determines what actual percentage value one obtains for incidence and prevalence. As we will see below, minor syndromes overlap with other complaints with a more physical emphasis.

## Chronic pain

Chronic pain syndromes may be focal or diffuse. The best known focal pain syndromes are probably pelvic pain and temporomandibular joint pain. The best known dif-

fuse pain syndrome is “fibromyalgia” (now the term preferred to the earlier fibrositis): fibromyalgia is chronic widespread pain and tenderness (the latter manifested as multiple tender points). Physical investigations tend to be negative. Increased rates of psychiatric disorders, particularly depressive, anxiety, and somatoform disorders, are apparent in clinic and community populations. Depression may be associated with the onset and persistence of fibromyalgia symptoms. Seen from one perspective, fibromyalgia is sometimes seen as the somatic expression of psychological distress—somatization. Although this is as much a restatement of the problem as a convincing solution to it. Furthermore, deriving as it does from Freud’s formulation of conversion syndromes, it carries the pejorative implication that such symptoms are hysterical (see ref 38 for an extreme statement of that view). An alternative view accepts that somatic symptoms are simply part of the depressive syndrome, perhaps magnified as an individual difference in some subgroups. This would predict a necessary overlap with depression, and a potentially shared etiology. The evidence for this might proceed from heritability, biology, and treatment similarities. The pattern within families indeed suggests that fibromyalgia is a depressive spectrum disorder.<sup>39</sup> Other similarities with the depressive phenotype include cognitive impairments<sup>40</sup> and disorders of the hypothalamo-pituitary axis.<sup>41</sup> Finally, the symptoms of fibromyalgia are responsive to antidepressants.<sup>42</sup>

## Chronic fatigue

Chronic fatigue syndrome (CFS) has proved to be an even more controversial diagnosis. The complaint of fatigue is common in community surveys, as indeed is that of low spirits or mild depression. The number of somatization symptoms and history of a dysphoric episode are the two strongest predictors of new onset of fatigue as well as recurrent/chronic fatigue over a 13-year follow-up interval in the Epidemiological Catchment Area (ECA) study. A history of unexplained fatigue at baseline was also a very high risk for new-onset major depression compared with those who never reported such fatigue, (RR = 28.4; 95% CI, 11.7, 68.0).<sup>43</sup>

The etiology of chronic fatigue is complex and heterogeneous. Data for “interfering fatigue” (IF) has been obtained on 7740 individual twins giving a prevalence of 9.9% in the previous year. IF was significantly associated with 42 of 52 potential correlates! There were two broad clusters:

- Major depression, generalized anxiety disorder, and neuroticism;
- Beliefs of ill health coexisting with alcoholism and stressful life events.

Genetic effects may be particularly important in women, and shared environmental effects in men.<sup>44</sup>

Clinic samples show a similarly heterogeneous picture. In women, chronic fatigue syndrome, fibromyalgia (FM), and multiple chemical sensitivity (MCS) show mutual comorbidity: of 163 women with CFS, 37% also met criteria for FM, and 33% met criteria for MCS. Patients with additional illness were more likely to have major depression and a higher risk of psychiatric morbidity compared with patients in the CFS only group.<sup>45</sup> This offers support for the notion of a single syndrome, perhaps with weakly distinct dimensions. Indeed, a larger statistical analysis of 646 patients who met accepted criteria for CFS and/or FM, suggested four latent classes differing in a graded fashion (rather than qualitatively) for symptom endorsements, premorbid characteristics, and comorbidity with panic disorder and major depression. CFS and FM appear to have more common points than they do differences.<sup>46</sup>

The relationship between major depression and severe chronic fatigue can be investigated biologically. Fatigue is of course a common symptom of depression. The findings from investigation of neuropsychological function echo the pattern of broad similarities and some potentially defining differences: depressed patients showed marked diurnal variation in motor function and more severe memory impairment.<sup>47</sup> Patients with chronic fatigue syndrome also show a specific sensitivity to the effects of exertion on effortful cognitive functioning, not seen in major depression. This occurs despite subjective and objective evidence of effort allocation in chronic fatigue syndrome. It suggests that patients have reduced working memory capacity, or a greater demand to monitor cognitive processes, or both.<sup>48</sup>

Comorbidity is also seen with irritable bowel syndrome (IBS). A systematic review of all the comorbidity studies of IBS<sup>49</sup> showed that the disorders with the best-documented association were fibromyalgia (median of 49%

have IBS), chronic fatigue syndrome (51%), temporomandibular joint disorder (64%), and chronic pelvic pain (50%). Major depression, anxiety, and other psychiatric disorders occurred in up to 94% of IBS cases.

The treatment of these conditions is as controversial as their diagnosis has often been. There are advocates of antidepressants, graded exercise, and cognitive behavior therapy (CBT). In some cases it is confusing. Thus, in one trial, CBT was shown to be superior to a more simple intervention.<sup>50</sup> In another, it was comparable to counseling.<sup>51</sup> The evidence supporting all the available interventions remains limited<sup>52</sup> and the cost of providing them potentially quite high. Antidepressants are probably widely prescribed, although their value in primary care remains uncertain.

## Conclusion

The challenge of the mood disorders lies in their apparently rising incidence and prevalence, the realization that long-term disability and even mortality is likely to be increasingly evident, and the need for better delivery of more effective treatments. Their association with other disorders may provide clues to etiology, especially relating to brain mechanisms underlying reward and stress/autonomic regulation. The greatest uncertainty relates to their co-occurrence with somatic syndromes which are common and poorly understood. There is a risk that the ubiquitous use of the term depression is becoming potentially counterproductive. There is a danger that, just as the authenticity of cases of functional disturbance or somatization is frequently doubted, so depression diagnoses now come to be seen as little more than endorsements of minor distress. This may do a disservice not only to those individuals whose minor syndromes are major to them, but also those patients with more severe depression whose treatment may be difficult and whose suffering may be discounted. □

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## La depresión y síntomas y enfermedades físicas asociadas

La depresión puede asociarse con virtualmente todos los otros diagnósticos físicos y psiquiátricos. La enfermedad física aumenta el riesgo de desarrollar una enfermedad depresiva grave. En términos generales existen dos mecanismos diferentes. El más obvio tiene un mecanismo psicológico o cognitivo. De esta manera, la enfermedad puede constituir en sí misma el acontecimiento de vida o traducirse en una dificultad crónica que gatilla un episodio depresivo en un individuo vulnerable. En segundo lugar, parecen existir asociaciones más específicas entre la depresión y ciertos trastornos físicos. Estas pueden resultar de especial interés etiológico. Los mejores ejemplos son probablemente el accidente vascular cerebral y la enfermedad cardiovascular. Finalmente, la depresión mayor, pero especialmente la depresión menor, la distimia y los síntomas depresivos aparecen junto con otras manifestaciones del estrés humano con el cual los pacientes se presentan a sus médicos. Dichas presentaciones somáticas prueban la distinción convencional entre trastorno físico y mental, y constituyen una fuente perenne de controversia.

## Dépression, symptômes et troubles physiques associés

En pratique, la dépression peut être concomitante de tous les autres troubles physiques et psychiatriques. Les troubles physiques augmentent le risque de développer une dépression sévère. Il existe deux sortes de mécanismes généralement différents. Le plus évident est un mécanisme psychologique ou cognitif. La maladie peut donc être à l'origine de l'événement de vie ou d'une difficulté chronique qui déclenche un épisode dépressif chez un individu vulnérable. Des associations plus spécifiques semblent exister secondairement entre la dépression et les troubles physiques particuliers. Ceci peut s'avérer d'un intérêt étiologique spécifique. Les accidents vasculaires cérébraux et la maladie cardiovasculaire en sont probablement le meilleur exemple. Finalement, la dépression majeure mais surtout la dépression mineure, la dysthymie et les symptômes dépressifs se fondent avec d'autres manifestations de souffrance humaine présentées aux médecins par leurs patients. Ces tableaux somatiques tentent de distinguer les troubles physiques et mentaux et sont une source éternelle de controverses.

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